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Association of N-Terminal Pro-Brain Natriuretic Peptide with Cognitive Function and Depression in Elderly People with Type 2 Diabetes

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Abstract

Background: Type 2 diabetes mellitus is associated with risk of congestive heart failure (CHF), cognitive dysfunction and depression. CHF itself is linked both to poor cognition and depression. The ventricular N-terminal pro-brain natriuretic peptide (NT-proBNP) is a marker of CHF, suggesting potential as a marker for cognitive impairment and/or depression. This was tested in the Edinburgh Type 2 Diabetes Study (ET2DS).

Methodology and Principal Findings: Cross-sectional analysis of 1066 men and women aged 60–75 with type 2 diabetes. Results from seven neuropsychological tests were combined in a standardised general cognitive ability factor, 'g'. A vocabulary-based test estimated pre-morbid cognitive ability. The Hospital Anxiety and Depression Scale (HADS) assessed possible depression. After adjustment for age and sex, raised plasma NT-proBNP was weakly associated with lower 'g' and higher depression scores (β -0.09 , 95% CI -0.13 to -0.03 , $p=0.004$ and β 0.08 , 95% CI 0.04 to 0.12 , $p<0.001$, respectively). Comparing extreme quintiles of NT-proBNP, subjects in the highest quintile were more likely to have reduced cognitive ability (within the lowest tertile of 'g') and 'possible' depression (HADS depression ≥ 8) (OR 1.80; 95% CI: 1.20, 2.70; $p=0.005$ and OR 2.18; 95% CI: 1.28, 3.71; $p=0.004$, respectively). Associations persisted when pre-morbid ability was adjusted for, but as expected were no longer statistically significant following the adjustment for diabetes-related and vascular co-variables (β -0.02 , 95% CI -0.07 to 0.03 , $p>0.05$ for 'g'; β 0.03 , 95% CI -0.02 to 0.07 , $p>0.05$ for depression scores).

Conclusion: Raised plasma NT-proBNP was weakly but statistically significantly associated with poorer cognitive function and depression. The prospective phases of the ET2DS will help determine whether or not NT-proBNP can be considered a risk marker for subsequent cognitive impairment and incident depression and whether it provides additional information over and above traditional risk factors for these conditions.

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Introduction

People with type 2 diabetes are at around 1.5 to 2.5-fold increased risk of developing dementia [1,2], a disorder involving progressive cognitive, behavioural and motor deficits. Type 2 diabetes is also associated with an increased risk of age-associated cognitive decline, short of frank dementia [3], and with depression [4,5], a condition closely related to cognitive dysfunction. The underlying mechanisms responsible for these links are unclear.

Co-morbidity with congestive heart failure (CHF) is also prevalent in diabetes [6,7]; there appears to be a poorly defined bidirectional relationship between cardiac function and glucose metabolism. Cardiac stress initiates secretion of natriuretic

peptides from the ventricles [8], including N-terminal pro-brain natriuretic peptide (NT-proBNP) the inactive metabolite of the proBNP hormone. Higher circulating NT-proBNP concentrations in populations with diabetes compared with healthy adults have been reported [9,10].

There is some evidence in predominantly non-diabetic populations to suggest that BNP (with which circulating NT-proBNP is highly correlated [11]) is associated with poor cognitive ability. Raised natriuretic peptide concentrations have been related to low performance on measures screening for poor global cognitive functioning potentially indicative of dementia [12–14]. Raised natriuretic peptide concentrations are also found in cognitively impaired individuals [15,16] and may correlate with severity of

dementia [14,17]. In the only prospective investigation to date, proBNP predicted dementia at 5-year follow-up [18].

Evidence also indicates raised NT-proBNP in individuals with major depressive disorder (MDD) and correlations between NT-proBNP and number of depressive symptoms in healthy populations [19] and in those with cardiovascular disease [20–22]. Further, left ventricular dysfunction has been associated with poor cognition [23–25] and depression [25]. However, overall evidence is inconclusive, with several studies failing to find a statistically significant association of NT-proBNP with depression or quality of life [26–29], with cognitive function [30,31], or dementia [15].

Given these findings, NT-proBNP could function as a biomarker of accelerated cognitive aging and depression in people with type 2 diabetes. High prevalence of cognitive and mood disorders in type 2 diabetes offers an interesting and novel opportunity to study the relationship between natriuretic peptides, acting as a proxy for cardiac stress, and cognitive function and depression. The present study aims to assess the association of NT-proBNP with level of cognitive ability, with level of ability relative to estimated peak pre-morbid ability, and with depressive symptoms, in a large, representative cohort of elderly patients with the full spectrum of severity of type 2 diabetes (the Edinburgh Type 2 Diabetes Study, ET2DS).

Methods

Study Population

Data from the cross-sectional, baseline phase of the prospective ET2DS were analysed. Details of the recruitment and examination for the ET2DS have been reported previously [32]. In brief, in 2006/7, 1066 community-dwelling men and women with type 2 diabetes mellitus, aged 60 to 75 years and living in the Lothian area of Scotland, UK, were selected at random from a comprehensive register of patients with diabetes attending primary or secondary care in this region. Subjects underwent detailed physical and cognitive examinations in a dedicated research clinic by specially trained nurses using standard operating procedures.

Ethics Statement

Assessments complied with the ethical rules of the Declaration of Helsinki. Ethical approval for the study was obtained from the Lothian Medical Research Ethics Committee, and all participants gave written informed consent.

Physical Examination

Participants were assessed by self-completion questionnaire and physical examination for a range of demographic and clinical characteristics. Diabetes-related measurements included plasma HbA1c, fasting glucose, duration of diabetes and mode of treatment. Vascular measurements included systolic and diastolic brachial blood pressure, body mass index (BMI), waist-hip ratio (WHR), % body fat, smoking status, alcohol intake, total serum cholesterol and ankle brachial index (ABI). ABI is the ratio of systolic blood pressure in the ankle to the systolic blood pressure in the arm, and has been used as a measure both of peripheral arterial disease and more generalised subclinical atherosclerosis [33,34]. Pre-specified criteria were used to define prior myocardial infarction (MI), angina or stroke using a combination of self-report of a doctor diagnosis, WHO chest pain questionnaire, 12-lead ECG and linkage to hospital discharge records, as has been described in detail previously [35].

Cognitive and Mood Assessment

Seven neuropsychological tests measured various dimensions of cognitive ability. The Borkowski Verbal Fluency Test (BVFT) examined executive function. Immediate and delayed recall was assessed in the Logical Memory subtest (LM) of the Wechsler Memory Scale 3rd Edition (WMS-III). The Faces subtest of the WMS-III was a measure of non-verbal memory. Mental flexibility and visual attention were examined by the Trail-Making Test B (TMT-B). Several subtests of the Wechsler Adult Intelligence Scale 3rd Edition (WAIS-III) were administered: Digit Symbol Coding (DSC; speed of information processing), Letter Number Sequencing (LNS; working memory) and the Matrix Reasoning test (MR; non-verbal reasoning). Vocabulary ('crystallised' intelligence) was measured using the combined junior and senior Mill Hill Vocabulary scale (MHVS) synonyms. As the results of vocabulary tests show very little mean decline with ageing, they can be used to estimate peak, prior cognitive ability [36]. When late-life cognitive ability scores are adjusted for vocabulary-based test scores, the residuals correlate highly with actual measures of cognitive change over a lifetime [37]. A score of below 24 out of 30 on the Mini-Mental-State Examination (MMSE; [38]) indicated presence of possible dementia. Presence of depression and anxiety was assessed on the Hospital Anxiety and Depression Scale (HADS; [39]). Responses were made on four-point scales, with maximum scores of 21 on each of two subscales, the HADS-A and HADS-D. In addition to the use of the HADS-D as a continuous outcome, 'possible cases' of clinical depression (HADS-D ≥ 8) were identified. Both these applications of the HADS are widely employed in the literature [40], and the cut-point of 8 has been shown to have high sensitivity and specificity [41]. A majority of participants completed the entire cognitive test battery and mood assessment ($n = 1048$ to 1065 for individual tests), and provided data on all physical measures ($n = 1028$ to 1066). Incompleteness was mainly due to physical difficulty rather than test refusal.

Measurement of NT-proBNP

Fasting blood samples were taken at the research clinic, and plasma was frozen for storage. Plasma NT-proBNP concentrations were determined using the Elecsys 2010 electrochemiluminescence method (Roche Diagnostics, Burgess Hill, UK) calibrated using the manufacturer's reagents. Manufacturer's controls were used with limits of acceptability defined by the manufacturer. Low control CV was 6.7% and high control CV was 4.9%.

Statistical Methods

Distribution of values was skewed for NT-proBNP, HADS-D, and TMT-B. These variables were transformed to their natural logarithm values.

Individuals who perform well on one cognitive test tend to perform well on another, so that different cognitive tests load on a single common factor, ' g ' [42]. Principal component analysis revealed that all seven cognitive tests (LM, Faces, MR, DSC, TMT-B, LNS, BVFT) could indeed be captured by the single standardised factor, ' g '.

Initial two-tailed Pearson correlations tested associations of NT-proBNP with other clinical measures, cognitive outcome and HADS depression scores. Mean NT-proBNP levels were compared between groups with suspected dementia (MMSE < 24), and between those with suspected clinical depression (HADS-D score ≥ 8) and those without.

In exploratory univariate analyses, mean ' g ' and HADS depression scores were compared between the highest and the lower four quintile NT-proBNP groups. The likelihood of low cognitive functioning (scoring in the lowest versus intermediate or

highest tertiles of 'g') and of suspected clinical depression were calculated for the highest quintile NT-proBNP as an example of a group with raised NT-proBNP levels.

Scores on the different cognitive tests were also treated as individual continuous outcome variables. NT-proBNP was modelled on each of these, 'g', and HADS depression, adjusting for potential confounders in staged and cumulative linear regression analyses. Confounders were selected on the basis of results from exploratory univariate analyses and reports in the literature of confounding or mediating roles in the relationship of NT-proBNP with cognition or depression. Results from the regression analyses were presented as β regression coefficients to show the direction and strength of the associations, signifying the change in cognitive and depression scores for each unit increase in NT-proBNP.

For cognitive outcome variables, only age and sex were controlled for in a first model. Estimated pre-morbid cognitive ability (MHVS) was entered in a second stage, before the addition of diabetes-related and cardiovascular risk factor variables (smoking status, blood pressure, BMI, HbA1c, cholesterol and mode of treatment). MI, angina, stroke and ankle brachial index (ABI) were then entered, but had not previously been included in order to avoid over-adjustment. HADS depression scores were added in a final model in order to determine the potential independence of NT-proBNP associations with cognition and depression. The first two modelling steps were also followed for the HADS depression outcome. In a third step, HbA1c and mode of treatment were controlled for. Cardiovascular disease variables were only added into the model in a final step, again in order to avoid over-adjustment given the role of NT-proBNP as a marker of cardiovascular disease. Analyses were performed using SPSS for Windows, version 14.0 (IBM Corporation, New York).

Results

Cohort characteristics and classical risk factors

Characteristics of the ET2DS participants are shown in Table 1. The study population ($n = 1066$) has been shown previously to be largely representative of all people invited to participate in the study ($n = 5454$) and therefore of the target population of older men and women with type 2 diabetes living in the general population [35]. Mean age was 67.9 years. Mean plasma NT-proBNP levels were similar in men and women (geometric means 79 pg/ml ± 3 vs 84 pg/ml ± 3 ; $p = 0.41$ and correlated positively with age ($r = 0.25$; $p < 0.001$). Controlling for age and sex, NT-proBNP was significantly associated with the following variables: duration of diabetes ($r = 0.14$; $p < 0.001$), diastolic blood pressure ($r = -0.09$; $p = 0.008$), ABI ($r = -0.14$; $p < 0.001$), BMI ($r = 0.11$; $p < 0.001$) and cholesterol ($r = -0.10$; $p = 0.005$), but not with HbA1c, plasma glucose or systolic blood pressure ($p > 0.05$). Mean levels differed between individuals with MI, stroke or angina and those without ($p < 0.001$ respectively), but not between smokers and non-smokers ($p > 0.05$).

NT-proBNP associations with cognitive performance

After controlling for age and sex, NT-proBNP was weakly but statistically significantly correlated with decreased performance on MHVS, Logical Memory, TMT-B, DSC, MR, the general ability factor 'g' and HADS depression. NT-proBNP levels accounted for $< 1\%$ of variance in cognitive test scores and 'g' ($r^2 = 0.005$ to 0.008), and for 1.7% of depression scores. ($r^2 = 0.017$; Table 2). NT-proBNP was not significantly different in the small group of participants with possible dementia (MMSE < 24 , $n = 30$) compared with higher scoring individuals (geometric mean 106 pg/ml ± 3 vs 81 pg/ml ± 3 , $p = 0.24$). However, the group with possible

clinical depression (HADS depression score ≥ 8 , $n = 78$) had lower mean MMSE scores (geometric means 27.80 ± 1.08 vs 28.28 ± 1.08 , $p = 0.052$, Cohen's $d = 0.24$) and higher NT-proBNP levels (geometric mean 107 pg/ml ± 3 vs 80 pg/ml ± 3 , $p = 0.03$, Cohen's $d = 0.28$) compared to the non-depressed group.

To further explore whether plasma NT-proBNP could be a marker of reduced cognitive function irrespective of other possible markers, we examined differences in cognitive ability across quintiles of NT-proBNP (geometric cutpoints were 29.70, 59.15, 100.48 and 217.02 pg/ml). An analysis of covariance with adjustment for age and sex suggested an overall trend across quintiles (adjusted mean 'g' = 0.02, 0.14, 0.13, -0.09 and -0.18 respectively; $p = 0.003$). Subjects in the highest quintile of NT-proBNP ($n = 199$) had lower 'g' than those in the remaining four quintiles ($n = 807$; adjusted means -0.18 versus 0.05 ; 95% CI for difference -0.39 , -0.08 ; $p = 0.003$). In unadjusted analyses comparing the highest quintile of NT-proBNP to all other quintiles, the odds ratios for low cognitive ability ('g' in the lowest tertile) was 2.14 (95% CI: 1.44, 3.18; $p < 0.001$). After adjustment for age and sex, the association was marginally attenuated to 1.80 (95% CI: 1.20, 2.70; $p = 0.005$).

For 'g' and each of the constituent cognitive tests, multiple regression analyses were carried out (Table 3). The initial model controlled for age and sex. Associations with NT-proBNP reached statistical significance for a number of cognitive tests (Logical Memory, TMT-B, DSC, MR), and 'g'. In a second step, pre-morbid cognitive ability (MHVS) was added into the model. The associations with TMT-B, DSC, MR, and 'g' remained statistically significant, and for Logical Memory approached significance. When a range of potential confounding and/or mediating variables, including conventional cardiovascular risk factors together with HbA1c and treatment type were added in a third model, only the association with Logical Memory remained statistically significant and also survived the further adjustment for previous cardiovascular disease and HADS depression in a final step.

NT-proBNP associations with depression

Adjusting for age and sex, HADS depression scores gradually increased across NT-proBNP quintiles (geometric mean scores were 2.77, 2.94, 3.19, 3.25 and 3.56 respectively; $p = 0.007$). The highest NT-proBNP quintile had higher mean depression scores compared with the lower four quintiles (95% CI 0.05, 0.28; $p = 0.006$). The age- and sex-adjusted odds ratio (OR) for possible clinical depression, comparing the highest versus the lower four quintiles, was 2.18 (95% CI 1.28, 3.71; $p = 0.004$).

Multivariable modelling was repeated for HADS depression. The age and sex adjusted association reached significance and survived additional adjustment for pre-morbid cognitive ability, as well as diabetes-associated variables. The association became non-significant following the addition of previous cardiovascular disease into the model (Table 4).

Discussion

This epidemiological study investigated the contribution of NT-proBNP levels to performance on a large battery of cognitive tests and symptoms of depression in older people with type 2 diabetes using one of the largest community-based study populations on this topic. Cognitive ability, measured by the standardised factor 'g', was lower, and depression higher, in patients with raised plasma NT-proBNP. Participants with peptide levels in the highest quintile of NT-proBNP distribution were almost two times more likely to have reduced cognitive ability (lowest tertile of 'g') and

Table 1. Baseline characteristics of the ET2DS population.

Variable	Mean \pm SD, median (quartile range) or n (%)
Age (years)	67.9 \pm 4.2
Male sex (%)	547 (51.3)
Duration of diabetes (years)	6 (3–11)
Treatment of diabetes with insulin +/- tablets	186 (17)
Treatment with tablets alone	679 (64)
Treatment with dietary change alone	200 (19)
HbA1c (%)	7.4 \pm 1.1
Fasting plasma glucose (mmol/L)	7.6 \pm 2.1
Systolic BP (mmHg)	133 \pm 16
Diastolic BP (mmHg)	69 \pm 9
Myocardial infarction	150 (14)
Angina	298 (28)
Stroke	62 (6)
ABI	0.98 \pm 0.21
BMI (kg/m ²)	31.4 \pm 5.7
Total cholesterol (mmol/L)	4.3 \pm 0.9
Smoking (current) (%)	153 (14.4)
NT-proBNP (pg/ml)	75 (37–169)
Hospital Anxiety and Depression Questionnaire (HADS): Depression score	3 (1–6)
HADS depression score \geq 8	78 (7.3)
Mini-Mental State Examination $<$ 24/30 (%)	30 (2.9)
Trail-Making Test B	104 (81–138)
Matrix Reasoning	12.8 \pm 5.3
Digit Symbol Coding	49.2 \pm 14.8
Verbal Fluency Test	36.9 \pm 12.8
Letter Number Sequencing	9.7 \pm 2.8
Faces	65.8 \pm 7.9
Logical Memory	25.2 \pm 8.2
<i>g</i>	0.00 \pm 1.00
Mill Hill Vocabulary Scale	30.9 \pm 5.2

Mean \pm SD is given for normally distributed variables.

Median (quartile range) is given for non-normally distributed variables.

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were more than two times more likely to have possible clinical depression following the adjustment for age and sex, compared with the remaining population, but associations of NT-proBNP with '*g*' and depression scores no longer reached statistical significance when diabetes-related and vascular co-variables were additionally controlled for.

Although not the main focus of the present investigation, raised NT-proBNP was also found to be associated with poorer pre-morbid cognitive ability. This finding could cast doubt over a causal relationship between cardiac stress (as measured by natriuretic peptides) and late-life cognitive ability in people with diabetes, since 'reverse causation' and confounding are possible explanations [43]. Low early life cognitive ability leads to lower late-life ability, and exposes individuals to poor lifestyle choices, health problems with associated raised biomarker levels, and earlier death [44]. However, the reported weak associations between NT-proBNP and current cognitive ability remained significant when pre-morbid ability was controlled for.

The association between reduced late-life cognitive ability and plasma NT-proBNP is consistent with previous studies on predominantly non-diabetic populations [12–14]. However, previous studies have predominantly used simple screening instruments, such as the MMSE, to measure cognitive function. Our use of a general ability factor derived from a number of different cognitive tests is unique in the literature on NT-proBNP and cognition. Although the age- and sex-adjusted odds of reduced cognitive ability for the high NT-proBNP group were comparable to those reported by Daniels et al. [12], the multivariate associations between NT-proBNP and cognitive scores were relatively weak compared with some previous investigations [13,14]. Peptide levels were also similar in subjects with and without suspected dementia determined using the MMSE (MMSE $<$ 24) compared with others. This finding is consistent with previous studies [15,30,31], but may reflect flaws in the use of the MMSE, designed to screen for dementia, as a measure of milder forms of cognitive impairment [45].

Table 2. Age and sex-adjusted two- tailed partial correlations of NT-proBNP with cognitive and depression scores.

	Partial correlation coefficient	p-value
Mill-Hill Vocabulary Scale	−0.07	0.042
Borkowski Verbal Fluency	<0.01	0.963
Logical Memory	−0.08	0.015
Faces	−0.05	0.139
ln(Trail-Making-Test-B)	0.08	0.012
Digit Symbol Coding	−0.09	0.006
Letter Number Sequencing	−0.05	0.146
Matrix Reasoning	−0.08	0.010
g	−0.09	0.007
ln(HADS depression)	0.13	<0.001

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Associations between NT-proBNP and deficits in specific cognitive domains were also explored. When age and sex were controlled for, peptide levels were unrelated to performance on BVFT, Faces or LNS, but were associated with poor performance on Logical Memory, TMT-B, DSC and MR. Furthermore, these relatively weak associations (except that for Logical Memory, for which a trend was observed) remained statistically significant following adjustment for estimated pre-morbid ability. The finding of inverse associations between peptide levels and performance on the TMT-B test of visual attention and the Matrix Reasoning test of non-verbal reasoning is consistent with investigations in non-diabetic populations [12,14]. NT-proBNP was unrelated to verbal fluency (BVFT) both in the present study and in Gunstad et al. [14]. Associations in Daniels et al. [12] also only reached statistical significance when analyses were largely unadjusted. NT-proBNP

has not previously been investigated in relation to nonverbal memory (Faces), speed of information processing (DSC) or working memory (LNS), of which we found an association only with speed of processing. It must be noted that since a large number of analyses were carried out, it is possible that the statistically significant associations arose through type I error. Further studies are required to confirm or refute these findings.

For any disease, the identification of biomarkers indicating increased risk of complications and co-morbidities is vital to allow identification of high risk individuals. Despite high prevalence of vascular disease and associated high average NT-proBNP levels in people with type 2 diabetes [9,10], as well as high prevalences of cognitive and mood disorders, to our knowledge, this is the first investigation to focus on the relationship of NT-proBNP with cognitive function and mood in type 2 diabetes.

The association of natriuretic peptides with late cognitive ability may well reflect underlying cardiac stress and associated vascular disease, rather than any direct causal relationship. This is supported by the attenuation of the relationship between cognitive ability and NT-proBNP following the adjustment for a range of cardiovascular risk factors and cardiovascular disease, which rendered it statistically non-significant. A weak association between NT-proBNP and the Logical Memory test (which measures verbal declarative memory through recall of a short story and is particularly sensitive to progression of type 2 diabetes [46]) was unique, in that it was not attenuated by the adjustment for cardiovascular or diabetes-associated variables, or HADS depression scores. Despite the possibility that the result represents a type I error, it is an intriguing finding which merits further investigation.

Raised NT-proBNP was also associated with high depression scores, supporting previous findings from non-diabetic populations [19–22]. The relative weakness of the associations is consistent with one previous report [22], although associations overall tend to be larger [19–21]. Despite predicting high risk of future vascular disease and depression, low pre-morbid ability did not confound the association. Pathways linking depression and NT-proBNP levels have been suggested previously [19]. We found evidence

Table 3. Multivariate associations between NT-proBNP and cognitive test scores.

		MHVS	g	BVFT	LM	FACES	ln(TMT-B)	DSC	LNS	MR
Model 1a	β	−0.26	−0.09	0.02	−0.49	−0.31	0.03	−0.96	−0.10	−0.35
	95% CI	−0.54, 0.01	−0.13, −0.03**	−0.65, 0.69	−0.91, −0.06*	−0.71, 0.10	0.01, 0.05*	−1.71, −0.20**	−0.25, 0.04	−0.62, −0.08**
Model 2b	β		−0.05	0.28	−0.36	−0.20	0.02	−0.69	−0.04	−0.25
	95% CI		−0.09, 0.00*	−0.33, −0.89	−0.75, 0.04	−0.59, 0.19	0.00, 0.04*	−1.38, 0.00*	−0.18, 0.90	−0.50, −0.01*
Model 3c	β		−0.04	0.38	−0.48	−0.15	0.02	−0.26	−0.04	−0.23
	95% CI		−0.08, 0.01	−0.26, 1.01	−0.89, −0.07*	−0.56, 0.26	0.00, 0.04	−0.98, 0.46	−0.17, 0.10	−0.48, 0.02
Model 4d	β		−0.02	0.18	−0.57	−0.01	0.02	0.19	−0.01	−0.15
	95% CI		−0.07, 0.03	−0.52, 0.87	−1.02, −0.11*	−0.46, 0.44	−0.01, 0.04	−0.60, 0.98	−0.16, 0.15	−0.43, 0.13
Model 5e	β		−0.02	0.16	−0.56	−0.03	0.01	0.26	0.01	−0.14
	95% CI		−0.06, 0.03	−0.56, 0.88	−1.03, −0.08*	−0.50, 0.44	−0.01, 0.04	−0.54, 1.07	−0.15, 0.16	−0.42, 0.15

The β scores are regression coefficients.^aadjusted for age and sex.^badjusted for +MHVS.^cadjusted for + smoking status, blood pressure, BMI, HbA1c, cholesterol, mode of treatment.^dadjusted for + MI, angina, stroke, ABL.^eadjusted for + ln(HADS depression).

*significant at 0.05 level.

**significant at 0.01 level.

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Table 4. Multivariate associations between NT-proBNP and depression scores.

		ln(HADS depression)
Model 1^a	β	0.08
	95% CI	0.04, 0.12**
Model 2^b	β	0.08
	95% CI	0.04, 0.12**
Model 3^c	β	0.07
	95% CI	0.03, 0.11*
Model 4^d	β	0.03
	95% CI	−0.02, 0.07

The β scores are regression coefficients.

^aadjusted for age and sex.

^badjusted for +MHVS.

^cadjusted for + HbA1c, mode of treatment.

^dadjusted for + MI, angina, stroke, ABL.

*significant at 0.05 level.

**significant at 0.01 level.

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against this, as the association became non-significant when previous cardiovascular disease was controlled for. Depression is associated with a harmful lifestyle and subsequent endothelial damage, and also accelerates the progression of cardiac illness through effects on the hypothalamic-pituitary adrenal (HPA) axis, increasing the risk of heart failure [47]. Conversely, heart failure and other chronic illness initiate symptoms of depression, including hypersomnia, fatigue and loss of energy [48], constructs included in the HADS questionnaire.

Overall, the clinical relevance of natriuretic peptides as biomarkers for poor cognitive function and depression is unclear. Despite a relatively weak multivariate association, individuals in the highest NT-proBNP quintile were substantially more likely to have reduced cognitive ability and depression compared with the remaining population. NT-proBNP may function as a biomarker of subclinical cerebrovascular disease particularly in individuals who experience cardiac stress. This extends its well-established role as a predictor of cardiovascular and cerebrovascular events [49]. Mirroring a greater ability of natriuretic peptides compared with other biomarkers, such as c-reactive protein (CRP), to predict

these outcomes [50], the association of NT-proBNP with cognitive function in the present study was also stronger than that of CRP with cognitive function in a previous analysis [35].

A strength of the current study was the ability to adjust for a wide variety of variables, both those which are commonly controlled for (e.g., age), and those which may be confounding or mediating factors underlying the relationship between NT-proBNP and cognitive ability (e.g., vascular risk factors; cardiovascular disease). Due to the large size of the study, results are more robust than those of previous investigations carried out on smaller scales [15–17] and the analysis had high power to detect even weak associations, although admittedly, the clinical relevance of such associations is debatable. The latter was reflected in the conservative interpretation of statistically significant results. The cross-sectional nature of the study and the resulting unclear direction of the reported associations is a weakness of the study, although this was partly offset by our adjustment for pre-morbid cognitive ability. The MHVS as a measure of pre-morbid ability is advantageous over the often used level of education, which is subject to self-report bias.

In conclusion, we found some evidence for NT-proBNP as a biomarker of low cognitive ability and depression in elderly people with type 2 diabetes, although the associations were relatively weak and were largely explained by previous cardiovascular disease. The value of NT-proBNP measurement over and above the assessment of traditional markers of cognitive dysfunction and depression remains unclear, and further studies on its relationship with these disorders are needed. Analysis of the second wave of data of the prospective ET2DS will provide an ideal opportunity to investigate the associations of natriuretic peptide levels with risk of subsequent cognitive decline and the development of depression.

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Author Contributions

Conceived and designed the experiments: JFP MWJS. Performed the experiments: IJD NS PW RMR. Analyzed the data: IF. Wrote the paper: IF NS PW RMR IJD MWJS JFP.

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